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Environmental Cadmium and Lead Exposures and Hearing Loss in US Adults: the National Health and Nutrition Examination Survey, 1999 to 2004

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ABBREVIATIONS:

BMI, body mass index

Cd, Cadmium

CI , confidence interval

MEC, mobile examination center

NHANES, National Health and Nutrition Examination Survey

Pb, Lead

PTA , Pure-Tone Average

ABSTRACT

Background. Although cadmium and lead are known risk factors for hearing loss in animal models, few epidemiologic studies have been conducted on their associations with hearing ability in the general population.

Objectives. We investigated the associations between blood cadmium and lead exposure and hearing loss in the U.S. general population, while controlling for noise and other major risk factors contributing to hearing loss.

Methods. We examined 3,698 adults aged 20 to 69 years from the National Health and Nutrition Examination Survey (NHANES) 1999-2004. Pure-tone averages (PTA) of hearing thresholds at frequencies at 0.5, 1, 2 and 4 kHz were computed, and hearing loss was defined as a PTA greater than 25 dB in either ear.

Results. The weighted geometric means of blood cadmium and lead were 0.40 (95% confidence interval (CI), 0.39 to 0.42) μg/L and 1.54 (1.49 to 1.60) μg/dL, respectively. After adjustment for sociodemographic/clinical risk factors and exposure to occupational and non-occupational noise, the highest (vs. lowest) quintiles of cadmium and lead were associated with 13.8% (4.6%, 23.8%) and 18.6% (7.4%, 31.1%) increases in PTA, respectively (p-trends<0.05).

Conclusions. These results suggest that low-level exposure to cadmium and lead found in the general U.S. population may be important risk factors for hearing loss. Our findings support efforts to reduce environmental cadmium and lead exposures.

INTRODUCTION

Hearing loss is one of the most common chronic disabling conditions among older adults (Bainbridge et al. 2008). More than 35 million people aged 18 years and older suffer from hearing loss in the U.S. in 2008, and the prevalence of hearing loss tends to increase dramatically with advancing age (Pleis et al 2006). Loud noise exposure at workplaces (Choi et al. 2012) and from firearms (Agrawal et al. 2009) is a well-established risk factor. A growing body of evidence suggests that exposure to ototoxic environmental and industrial chemicals also may impact the auditory system and lead to hearing loss (Agrawal et al. 2009; Bainbridge et al. 2008).

Experimental studies suggest that lead exposure induces degeneration in the inner ear receptor cells and latency in auditory nerve conduction velocity (Jones et al. 2008; Lasky et al. 1995; Yamamura et al. 1989) and that cadmium exposure causes apoptosis and alters the arrangement of inner ear receptor cells leading to an elevation in auditory thresholds (Kim et al. 2008; Ozcaglar et al. 2001). However, few epidemiologic studies of the association between low-level lead exposure and hearing loss have been conducted in the general population (Park et al. 2010), and there is only one epidemiologic study on cadmium exposure and hearing loss in US adolescents (Shargorodsky et al, 2011).

The aim of this study was to investigate the associations of environmental cadmium and lead exposure with hearing loss in representative U.S. adults who participated in the National Health and Nutrition Examination Survey (NHANES) 1999 to 2004**,** while controlling for important potential confounding factors, including occupational, firearm and recreational loud noise. We also estimated the joint effects of cadmium and lead, as well as effect modification by noise and other potential risk factors.

METHODS

Study Population

The NHANES 1999-2004, conducted by the National Center for Health Statistics (NCHS; Centers for Disease Control and Prevention (CDC), Atlanta, GA), is an ongoing series of cross-sectional surveys designed to obtain information from a representative sample of the civilian non-institutionalized US population. Data were collected through extensive household interviews to obtain information on health risk factors, including health behaviors, personal environment, and life style. In addition, physical examinations and medical history interviews were conducted at a specially equipped mobile examination center (MEC) (NCHS 2009). In NHANES 1999 to 2004, half of the participants aged 20 to 69 years were randomly assigned to the Audiometry Examination Component at MEC. Participants who used hearing aids that could not be removed for testing or who could not tolerate test headphones were excluded (NCHS 2005a). The initial sample size eligible for inclusion in the audiometric examination was 5,742 participants; 1,807 in 1999–2000, 2,046 in 2001–2002, and 1,889 in 2003–2004. An additional 479 participants were excluded because of non-responses or unreliable responses during the audiometric examination as described below.

For the present analysis we excluded participants with unilateral hearing loss (n=452) and those with missing information on blood cadmium or lead measurements (n=183), longest job held (n=376), firearm or recreational noise exposure (n=6), or other demographic or hearing-related variables (n=548) leaving a total of 3,698 observations. Compared to excluded participants with audiometric data, included participants had lower hearing thresholds and were less likely to be classified as having hearing loss, and were more likely to have completed high school and be non-Hispanic white (see Supplemental Material, Table S1). We excluded an

additional 76 participants (2.1%) who had hearing thresholds ≤ 0 dB (indicating better-than-normal hearing) from linear regression models (n=3,622) to better interpret regression results and to avoid adding a constant before log-transformation of hearing thresholds.

NHANES is a publicly available data set and all participants in NHANES provide written informed consent, consistent with approval by the National Center for Health Statistics Institutional Review Board.

Audiometric Measurement

Audiometry examinations were conducted in a sound-isolated room by health technicians trained by an audiologist certified by the National Institute for Occupational Safety and Health (NIOSH). Instrumentation for the Audiometry Component included an audiometer (Interacoustics Model AD226; Assens, Denmark) with standard headphones (TDH-39) and insert earphones (Etymotic EarTone 3A) (NCHS 2005a). Pure tone air conduction hearing thresholds were obtained for both ears at frequencies of 0.5 to 8 kHz over an intensity range of −10 to 120 decibels (dB). Results for examinees that did not respond to at least one frequency were classified as non-responses (n=476). As an additional measure of the quality of participant's responses, the 1 kHz frequency was tested twice in each ear, and audiograms with ≥ 10 dB difference between the tests were classified as unreliable responses (n=3) (NCHS 2005a).

We computed the hearing thresholds (dB) at speech frequencies as a pure tone average (PTA) of 0.5, 1, 2 and 4 kHz (Agrawal et al. 2009). Hearing loss was defined as a PTA ≥ 25 dB in either ear, consistent with the definition used by the World Health Organization (Ikeda et al. 2009).

Blood Cadmium and Lead Measurements

Blood cadmium and lead were measured at the Environmental Health Sciences Laboratory of the CDC National Center for Environmental Health (NCEH) after confirming the absence of background contamination in all collection and storage materials (NCEH 2001a). Cadmium and lead concentrations were measured by a simultaneous multielement atomic absorption spectrometer (Model SIMAA 6000l Perkin-Elmer, Waltham, MA) with Zeeman background correction in NHANES 1999-2002 (NCEH 2001a, b) and by an inductively coupled plasma-mass spectrometer (Model SCIEX 500; Perkin-Elmer, Shelton, CT) in NHANES 2003–2004 (NCEH 2004).

The detection limit for cadmium was 0.3 µg/L in NHANES 1999-2002 and 0.2 µg/L in NHANES 2003-2004, and the detection limit for lead was 0.3 µg/dL in all three NHANES cycles. Of study participants, 26% and 17% had cadmium concentrations below the detection limit in NHANES 1999-2002 and NHANES 2003-2004, respectively, and 0.8% of all participants had blood lead concentrations below the detection limit (NCHS 2004, 2006, 2007a). For these participants, we imputed a value equal to the detection limit divided by the square root of two (NCHS 2007b). Inter-assay coefficients of variation (CV) ranged from 6.1% to 7.3% and 4.1% to 4.4% for low and high blood cadmium QC pools, and from 4.0% to 7.0% and 3.1% to 3.2% for the low and high blood lead QC pools (NCEH 2001a, b, 2004).

Noise Exposure Assessments

Noise exposures (e.g. occupational, firearm, and recreational noise) may be important confounding factors in the associations of blood cadmium and lead with hearing loss. Direct measures of personal noise exposure are not available in the NHANES. Participants were

classified as exposed (versus unexposed) to non-occupational firearm noise if they indicated that they had ever been exposed to the noise of a firearm at least once a month for 1 year, and were classified as exposed to recreational noise if they indicated exposure to loud noise (e.g., power tools or loud music) at least once a month for 1 year, excluding exposure at work.

Occupational noise exposures were classified based on occupational noise estimates according to the job title for the longest job held by each participant. These estimates were based on a new occupational noise exposure assessment tool that uses the Occupational Network (O*NET) survey database (Choi et al. 2012). In brief, the longest job-related O*NET score (range as 1 to 5) was assigned to each participant as a proxy measure of personal occupational noise exposure. The median value of the occupational noise score was used to divide participants into low and high occupational noise exposure groups.

Demographic and Hearing-Related Variables

Information on other demographic and hearing-related variables was obtained during households interview or at the MEC. Body mass index (BMI) was calculated as dividing measured weight in kilograms by measured height in meters squared. Use of ototoxic medication was defined based on self-reported use of any aminoglycosides, loop diuretics, antineoplastic drugs, or nonsteroidal anti-inflammatory drugs during the past month. Smoking pack-years were computed, and participants were classified as nonsmokers, smokers with < 20 pack-years, or smokers with ≥ 20 pack-years. Hypertension was classified based on a self-reported physician diagnosis, current use of antihypertensive medication, or systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90 mm Hg at the time of examination. Diabetes mellitus was classified based on a self-reported physician diagnosis or current use of antihyperglycemic medication,

consistent with a previous study of diabetes and hearing loss (Bainbridge et al, 2008).

Statistical Analysis

All statistical analyses were performed using SAS survey procedures (SAS 9.2) and the R survey package (R 2.9.1) to account for the complex survey design and NHANES sample weights (NCHS 2005b). We computed 6-year sample weights per NCHS recommendations, which were adjusted for oversampling and non-participation of ethnic minorities, the elderly, and low income persons (NCHS 2009). Two-sided p-value <0.05 was considered statistical significance.

Hearing thresholds for PTA and individual frequencies were log-transformed to normalize distributions, and linear regression was used to model these outcomes. Blood lead and cadmium were log-transformed based on graphical evaluations suggesting improved fit compared with model estimates for non-transformed exposures, though estimates based on fully-adjusted natural spline models indicated non-linear associations with both log-transformed and non-transformed exposure variables (Supplemental Material, Figure S1). Therefore, we also modeled quintiles of blood cadmium and lead to better capture non-linear relationships. We estimated the percent change in hearing threshold for a doubling of the blood cadmium and blood lead as $(e^{(\ln 2 * ß)}-1)*100\%$, with 95% confidence intervals (CI) estimated as $(e^{(\ln 2 * (ß \pm 1.96 * SE))}-1)*100\%$, where ß and SE are the estimated regression coefficient and standard error. For quintiles, percent changes were estimated by comparing each of the upper four quintiles to the lowest quintile. P-values for a linear trend were computed by fitting the exposure quintile as an ordinal categorical variable coded using integer values (0 to 4). Logistic regression was used to estimate odds ratios (ORs) for the hearing loss defined as PTA ≥ 25 dB in one or both ears.

We used sequential models to assess the influence of potential confounders: model A was adjusted for age and age^2, sex, race/ethnicity [no-Hispanic white (reference), Mexican American, non-Hispanic black, other], education [<high school (reference), high school, > high school], BMI (continuous), ototoxic medication use (yes/no), cigarette smoking [never smoker (reference), <20 pack-years, ≥20 pack-years], hypertension (yes/no), type-2 diabetes (yes/no), and either blood lead or blood cadmium (for the corresponding cadmium or lead model); model B further adjusted for occupational noise exposure (O*NET score, continuous); and model C further adjusted for any non-occupational firearm noise (yes/no) and any recreational noise (yes/no). We kept hypertension and type-2 diabetes in model A although these variables could be potential intermediates between lead or cadmium exposure and hearing loss (Bainbridge et al. 2008; Chang et al. 2011) because the effect estimates between the models with and without adjustment for hypertension and diabetes were not much different (data not shown).

We also evaluated fully-adjusted associations with log-transformed PTA for subgroups defined by age (20-39, 40-59, ≥60 years), sex, BMI (<30, ≥30 kg/m^2), education, ototoxic medication use, cigarette smoking/pack-years, hypertension, diabetes, and occupational (<2.84, ≥2.84 O*NET score), firearm, and recreational noise exposure.

Joint effects of blood cadmium and lead with log-transformed PTA were examined in fully adjusted models using a combined categorical variable classified as low cadmium and low lead (reference), high cadmium and low lead, low cadmium and high lead, or high cadmium and high lead, with high and low categories defined based on median values for all study participants. Departures from additive joint effects [relative excess risk due to interaction (RERI)] and multiplicative joint effects were computed as recommended by Knol and VanderWeele (Knol and VanderWeele 2012) with the 95% CI for the RERI computed by the delta method (Hosmer and

Lemeshow, 1992).

RESULTS

Weighted means of age and PTA were 42.06 ± 0.28 years and 12.78 ± 0.24 dB, respectively (Supplemental Material, Table S2). Overall, 441 participants (11.9%) had hearing loss (PTA ≥ 25 dB in one or both ears). The age-adjusted geometric means (95% CIs) of blood cadmium and lead in the entire population were 0.40 (95% CI: 0.39, 0.42) µg/L and 1.54 (95% CI: 1.49, 1.60) µg/dL, respectively (Table 1). Compared with participants without hearing loss, those with hearing loss had significantly higher age-adjusted geometric mean blood cadmium (0.46; 95% CI: 0.42, 0.50 µg/L vs. 0.40; 95% CI: 0.38, 0.42 µg/L) and lead (1.72; 95% CI:1.62, 1.82 µg/dL vs. 1.52; 95% CI:1.47, 1.58 µg/dL) levels, respectively. Age-adjusted blood cadmium and lead levels differed by race/ethnicity and were higher in participants who were older, less educated, and ever smokers, and in those with high occupational noise exposure, BMI <30, and no diabetes. Blood lead levels also were higher in men, in participants who did not use ototoxic medications, and in participants with firearm noise exposure and those with recreational noise exposure. Blood cadmium levels were higher in women. Blood cadmium and lead levels were highly correlated (Spearman correlation coefficient=0.12, $p<0.001$).

Table 2 presents the estimated percent changes in PTA in association with blood cadmium and lead levels. Blood cadmium and lead levels, both as continuous variables and when modeled as quintiles, were positively associated with higher (poorer) hearing thresholds in all models. In the fully adjusted model (model C), subjects in the highest blood cadmium quintile had 13.8% (95% CI: 4.6, 23.8%) higher hearing thresholds than those in the lowest quintile. A doubling of blood cadmium was associated with a 4.1% (95% CI: 1.2,7.1%) increase in hearing

thresholds. Similarly, subjects in the highest blood lead quintile had 18.6% (95% CI: 7.4, 31.1%) higher hearing thresholds than those in the lowest quintile, and a doubling of blood lead was associated with a 5.4% (95% CI: 2.1, 8.8%) increase in hearing thresholds. Similar patterns of associations were observed between blood lead and individual frequencies of 0.5, 1, and 4 kHz (see Supplemental Material, Figure S2).

Table 3 shows the logistic regression results for hearing loss in different covariate-adjusted models. Trend tests for blood cadmium levels were significant in all models. Associations with blood lead levels were significant before, but not after, adjusting for noise exposures. Fully adjusted ORs for hearing loss comparing the highest versus the lowest blood cadmium and lead quintiles were 1.7 (95% CI: 1.1, 2.7) and 1.4 (95% CI: 0.8, 2.5), respectively.

We estimated the individual and joint effects of exposures to cadmium and lead on the hearing thresholds (Table 4). Participants with both high cadmium and lead exposures (vs. both low) had a 19.0% (95% CI: 9.7, 29.1%) increase in PTA that was consistent with additive effects of high cadmium only (7.3%; 95% CI: 0.4, 14.8%) and of high lead only (10.1%; 95% CI: 0.4, 20.8%). Estimates did not indicate departures from expectations for additive (RERI=1.6%; 95% CI: -9.4, 12.6%; p=0.78) or multiplicative joint effects (percent change of interaction term=0.7%; 95% CI: -8.9, 11.39%; p=0.89).

Figure 1 presents percent changes in PTA associated with a doubling of lead or cadmium by participant characteristics based on fully adjusted models. For blood cadmium, the association was stronger in non-Hispanic white compared with non-Hispanic black participants (p=0.02). For blood lead, the association was stronger in other race/ethnicity participants than in non-Hispanic whites (p=0.01). There were borderline significant differences in associations between blood lead and PTA comparing Mexican-American with non-Hispanic whites (p=0.05), and

participants not exposed to firearm noise with those who were (p=0.06).

DISCUSSION

In a representative sample of US adults who participated in NHANES 1999-2004, environmental cadmium and lead exposures were associated with hearing loss, even after adjustment for socioeconomic factors, noise exposures, and other potential risk factors. In addition, we observed positive dose-response relationships of hearing thresholds with blood cadmium and lead at levels currently observed in the general U.S. population. Compared with the lowest quintiles of cadmium and lead exposure, PTAs for participants in the highest quintiles were increase by 13.8% and 18.6%, respectively. These differences were consistent with estimated differences in PTAs associated with sex (18.4% higher in females vs. males), having diabetes (19.9%), ageing of 40 to 46 years (16.6%, participants mean age=42.1), and a two-unit increase of O*NET occupational noise scores (14.8%, corresponding to the noise exposure difference between 'Textile, apparel, and furnishings machine operators' versus 'Executive, administrators, and managers' occupation groups) (see Supplemental Material, Table S3).

Few epidemiologic studies have evaluated associations between low-level lead exposure and hearing outcomes. Our results extend limited evidence from occupational settings or studies of children (Discalzi et al. 1993; Forst et al. 1997; Schwartz and Otto 1991) to the general population. A previous study of 448 elderly community-dwelling men in Eastern Massachusetts reported a significant association between hearing loss and an interqurtile range increase in tibia and patella bone lead levels (OR=1.2; 95% CI: 0.9, 1.5 and OR=1.5; 95% CI: 1.1, 1.9, respectively) (Park et al. 2010). We estimated an increase in hearing thresholds of 4.1% (95% CI: 1.2, 7.1%) and OR for hearing loss of 1.1 (95% CI: 1.0, 1.3) with a doubling in blood lead,

which extends the body of evidence concerning lead and hearing loss to men and women in the U.S. as a whole.

To our knowledge, this is the first epidemiologic study to evaluate associations between hearing loss and cadmium exposure in adults. A few experimental studies have suggested possible mechanisms for cadmium ototoxicity. Studies using rats exposed to cadmium-contaminated drinking water suggested that cadmium can induce the generation of reactive oxygen species, loss of mitochondrial membrane depolarization, release of cytochrome c, activation of caspases, apoptosis, and the increase of extracellular signal-regulated kinase activation in auditory cells leading to an elevation in auditory thresholds (Kim et al. 2008; Ozcaglar et al. 2001). A recent study of US adolescents from NHANES 2005-2008 reported a significant association between urinary cadmium and low-frequencies hearing loss (defined as the average of thresholds at 0.5, 1, and 2 kHz > 15dB) (Shargorodsky et al, 2011).

The present study suggests that low-level exposures to cadmium and lead currently observed in the US general population may influence hearing health, and supports efforts to reduce environmental cadmium and lead exposures. Compared with participants with exposures in the first quintiles, those in the fifth quintiles of blood cadmium (0.80 – 8.50 μg/L) and blood lead (2.80 – 54.0 μg/dL) are at risk for poorer hearing ability. Occupational Safety and Health Administration (OSHA) safety standards are currently 44.5 nmol/L (5 μg/L) for cadmium and 1.93 μmol/L (38.6 μg/dL) for lead in whole blood (ATSDR 2010a, b). Very few participants in our study population exceeded these limits (0.11% and 0.05% of participants for cadmium and lead standards respectively); therefore, our findings may at least partly reflect effects on hearing below these levels. Evidence of possible effects of blood lead and cadmium at levels below current standards has also been reported for outcomes such as hypertension, chronic kidney

disease, and peripheral arterial disease (Guallar et al. 2006; Navas-Acien et al. 2009; Tellez-Plaza et al. 2007). In the general population, the primary sources of cadmium exposure are cigarette smoke, dietary intake (shellfish, offal, vegetables), and ambient air particularly in urban, industrial, and contaminated agricultural areas (Järup et al. 1998). Although primary historical sources of lead exposure (gasoline, solder, paint) have been phased out and environmental lead exposure has decreased considerably in the U.S. (Hu et al. 2007; Muntner et al. 2005), environmental exposure to low levels of both metals is still widespread (DHHS 2005; Muntner et al. 2005), and their accumulation in the body could influence the development of chronic diseases (Hu et al. 2007; Nordberg et al. 2007).

The present study found a joint effect of combined exposure to high cadmium and high lead on increased hearing thresholds, although formal hypotheses testing for additive and multiplicative interaction was not observed to be significant. The estimated joint effect of lead and cadmium was consistent with additive combined effects of the exposures on hearing resulting in an estimated 19% increase in thresholds in those with high lead and cadmium levels compared to those with low levels of exposure to both metals. Cadmium and lead share several similarities in molecular mechanisms implicated in toxicity. Both metals are divalent cations that interrupt sulfhydryl (-SH) containing enzymes, and induce reactive oxygen species increase via oxidation-reduction-inactive metal (Ercal et al. 2001; Vaziri and Khan 2007). They are also associated with changes in intracellular calcium homeostasis (Sabolić 2006), and finally co-exposure to both metals may act synergistically in auditory hair cell death and hearing loss. Few studies have estimated a joint effect of cadmium and lead exposures on other health outcomes. Navas-Acien et al. (2009) investigated the association of lead and cadmium with renal function in over 15,000 adults in the NHANES 1999-2006 (Navas-Acien et al. 2009), and observed a

significant interaction between cadmium and lead for albuminuria ($p=0.003$), based on the model including the product of the two log-transformed metals. Another study examining the associations of urinary cadmium and blood lead with reproductive hormones in over 700 young women in the NHANES III also found a stronger estimated effect by both high cadmium and lead in reducing inhibin B level, compared with high lead alone (Gollenberg et al. 2010).

Hypertension and diabetes may be potential causal intermediates rather than confounders since they are risk factors for hearing loss (Bainbridge et al. 2008; Chang et al. 2011) and are health outcomes that may be caused by cadmium and lead exposures (Hu et al. 1996; Schwartz et al. 2003; Tellez-Plaza et al. 2007). Therefore, we compared estimates from models that included all covariates (model A in Tables 2 and 3), except hypertension and diabetes and found the associations were not changed when hypertension and diabetes were excluded (data not shown).

Another possible explanation for the observed associations of cadmium and lead with shifts in hearing thresholds is that both metals exposures lower bone mineral density (BMD) (Alfvén et al. 2002; Chen et al. 2011) and affect chronic kidney disease (CKD) (Kim et al. 1996; Navas-Acien et al. 2009), which could mediate effects of these metals on hearing loss. This suggestion is supported by several bone disease studies which have observed a high correlation between BMD changes in cochlear capsule and sensorineural hearing loss (Guneri et al. 1996; Monsell et al. 1995) and kidney studies which indicated an association between reduced glomerular filtration rate (GFR; an indicator of CKD) and hearing loss (Vilayur et al. 2010).

Important strengths of this study include the use of data from a representative sample of the US general population, which supports generalization of the observed findings; adjustment for potentially important confounding factors, including occupational noise classified using a newly developed assessment tool based on O*NET (Choi et al. 2012), and non-occupational

noise exposures; and the use of NHANES, which are obtained using strict quality control procedures.

Several limitations in this study should be considered. The present study was conducted in a cross-sectional design which may raise an issue of validity of causal inferences between lead and cadmium exposures and hearing loss. Blood lead mainly reflects recent exposure, and therefore may not be a good biomarker to predict the long-term effect of low-level lead exposure, such as chronic diseases including hearing loss (Hu et al. 2007). Instead, bone lead has been suggested as a better biomarker of cumulative lead exposure (Hu et al. 2007), and a recent study conducted in Eastern Massachusetts showed a significant association between bone lead and age-related hearing loss (Park et al. 2010). Given that the measurement error of exposure is likely to be non-differential, we would expect that the true association might be larger. Blood cadmium generally reflects current exposure, whereas, urinary cadmium is considered cumulative exposure. However, both blood and urinary cadmium are considered the accumulated body burden in general populations with "low" level environmental exposure (Järup et al. 1998). We were not able to examine the association with urinary cadmium because urinary cadmium measures and audiometric tests were conducted in different subsets of NHANES 1999-2004 participants and the number that were included in both subsets is too small for a reliable statistical analysis.

In conclusion, the present study supports the hypothesis that environmental cadmium and lead exposures at levels currently observed in the US may increase the risk of hearing loss, the third leading chronic condition experienced by adults aged 65 and older (Yueh et al, 2003). Our findings support efforts to reduce environmental cadmium and lead exposures to effectively prevent or delay hearing loss in the general population.

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Table 1. Age-adjusted geometric means and 95% confidence intervals of blood cadmium and lead by participant characteristics (N=3698)

Characteristic	No. (%[a]) of participants	Blood Cadmium (ug/L),[b] (95% C.I.)	*P-value*[c]	Blood Lead (ug/dL),[b] (95% C.I.)	*P-value*[c]
Total	3698	0.40 (0.39-0.42)		1.54 (1.49-1.60)	
Hearing Loss					
No	3257 (88.8)	0.40 (0.38-0.42)		1.52 (1.47-1.58)	
Yes	441 (11.2)	0.46 (0.42-0.50)	*0.001*	1.72 (1.62-1.82)	*<.001*
Age *(y)*					
20-39	1650 (44.8)	0.36 (0.34-0 38)		1.23 (1.18-1.29)	
40-59	1385 (43.8)	0.44 (0.41-0.46)		1.75 (1.67-1.81)	
60-69	663 (11.3)	0.45 (0.42-0.48)	*0.007*	2.09 (1.98-2.21)	*0.004*
Sex					
Male	1729 (48.6)	0.38 (0.36-0.40)		1.94 (1.87-2.02)	
Female	1969 (51.4)	0.43 (0.41-0.45)	*<0.001*	1.24 (1.19-1.31)	*<.001*
Body mass index *(wtkg/htm)*					
< 30	2484 (69.0)	0.42 (0.39-0.44)		1.61 (1.54-1.69)	
≥ 30	1214 (31.0)	0.38 (0.36-0.40)	*0.003*	1.40 (1.34-1.47)	*<.001*
Race ethnicity					
Non-Hispanic White	1827 (72.5)	0.40 (0.38-0.42)		1.48 (1.42-1.55)	
Non-Hispanic Black	750 (10.5)	0.42 (0.39-0.45)		1.77 (1.68-1.87)	
Mexican American	805 (6.6)	0.39 (0.36-0.42)		1.81 (1.69-1.95)	
Other	316 (10.4)	0.46 (0.43-0.49)	*0.014*	1.60 (1.47-1.74)	*<.001*

Table 1 (Cont.)

Characteristic	No. (%[a]) of participants	Blood Cadmium (ug/L),[b] (95% C.I.)		*P-value*[c]	Blood Lead (ug/dL),[b] (95% C.I.)		*P-value*[c]
Education							
< High School	974 (16.6)	0.55	(0.51-0.58)		1.99	(1.89-2.11)	
High School	849 (25.1)	0.45	(0.42-0.48)		1.62	(1.53-1.71)	
> High School	1875 (58.3)	0.36	(0.34-0.37)	*<.001*	1.41	(1.35-1.47)	*<.001*
Ototoxic medication							
No	3132 (84.1)	0.40	(0.39-0.42)		1.59	(1.53-1.66)	
Yes	566 (15.9)	0.41	(0.37-0.45)	*0.981*	1.31	(1.23-1.39)	*<.001*
Cumulative cigarette pack-years							
Never	2105 (53.7)	0.29	(0.27-0.30)		1.33	(1.27-1.40)	
< 20	1183 (33.7)	0.58	(0.54-0.61)		1.81	(1.73-1.89)	
≥ 20	410 (12.5)	0.68	(0.61-0.76)	*<.001*	1.89	(1.78-2.01)	*<.001*
Current dx of hypertension							
No	2713 (76.8)	0.41	(0.39-0.43)		1.56	(1.50-1.62)	
Yes	985 (23.2)	0.38	(0.36-0.41)	*0.071*	1.49	(1.40-1.59)	*0.164*
Current dx of diabetes mellitus							
No	3485 (95.9)	0.41	(0.39-0.43)		1.56	(1.51-1.62)	
Yes	213 (4.1)	0.32	(0.28-0.37)	*<0.001*	1.20	(1.07-1.35)	*<.001*
Occupation noise exposure *(O*NET score)*							
Low (< 2.84)	1815 (52.7)	0.37	(0.35-0.38)		1.31	(1.25-1.38)	
High (> 2.84)	1883 (27.3)	0.45	(0.43-0.48)	*<.001*	1.85	(1.77-1.92)	*<.001*
Firearm noise exposure							
No	3468 (92.5)	0.40	(0.39-0.42)		1.52	(1.46-1.57)	
Yes	230 (7.5)	0.41	(0.36-0.47)	*0.872*	1.94	(1.72-2.18)	*<0.001*
Reacreation noise exposure							
No	2844 (74.0)	0.40	(0.38-0.42)		1.47	(1.41-1.54)	
Yes	854 (26.0)	0.42	(0.39-0.45)	*0.184*	1.77	(1.67-1.88)	*<.001*

[a]Weighted percentages from survey freq were presented.
[b]Geometric mean blood lead and cadmium levels (age-adjusted) were presented. For age groups, unadjusted lead and cadmium levels were presented.
[c]Survey *t*-test for binominal groups and Survey *Wald F*-tes*t* for categorical groups were used.

Table 2. Percent change (95% CIs) in hearing thresholds (dB) by blood cadmium and lead levels (N=3622)

Variables	No.	Model A[a]		Model B[b]		Model C[c]	
Cadmium							
Per doubling of Cadmium		4.38	(1.43, 7.41)	4.07	(1.09, 7.15)	4.13	(1.19, 7.15)
Cadmium Quintile *(ug/L)*							
Quintile 1 (0.10-0.20)	1013	0	(Reference)	0	(Reference)	0	(Reference)
Quintile 2 (0.30-0.30)	553	-1.02	(-8.75, 7.35)	-1.53	(-9.22, 6.81)	-1.22	(-8.86, 7.07)
Quintile 3 (0.40-0.40)	581	2.21	(-5.10, 10.08)	1.26	(-5.95, 9.02)	1.68	(-5.60, 9.53)
Quintile 4 (0.50-0.70)	785	7.07	(-1.07, 15.87)	6.53	(-1.58, 15.32)	6.69	(-1.48, 15.53)
Quintile 5 (0.80-8.50)	690	14.49	(5.17, 24.64)	13.42	(4.18, 23.48)	13.78	(4.55, 23.82)
P-Trend			*0.003*		*0.006*		*0.005*
Lead							
Per doubling of Lead		6.24	(2.88, 9.71)	5.68	(2.35, 9.13)	5.41	(2.12, 8.81)
Lead Quintile *(μg/dL)*							
Quintile 1 (0.20-0.80)	629	0	(Reference)	0	(Reference)	0	(Reference)
Quintile 2 (0.90-1.30)	842	-0.04	(-9.50, 10.41)	-0.06	(-9.51, 10.38)	-0.50	(-9.94, 9.93)
Quintile 3 (1.40-1.80)	679	7.30	(-3.05, 18.76)	7.11	(-3.23, 18.54)	6.51	(-3.76, 17.89)
Quintile 4 (1.90-2.70)	734	11.86	(0.97, 23.92)	11.01	(0.26, 22.91)	10.22	(-0.40, 21.97)
Quintile 5 (2.80-54.00)	738	21.13	(9.43, 34.09)	19.44	(7.96, 32.14)	18.63	(7.35, 31.09)
P-Trend			*<.001*		*<0.001*		*<0.001*

[a]Model A was adjusted for age, age^2, sex, race/ethnicity, education, body mass index, ototoxic medication, pack-years of cigarette smoke, hypertension, and diabetes. Cadmium models were further adjusted for lead; lead models were further adjusted for cadmium.
[b]Model B: Model A + further adjusted for occupation noise.
[c]Model C: Model B + further adjusted for recreation noise, and firearm noise.

Table 3. ORs (95% CIs) for hearing loss[a] by blood cadmium and lead levels (N=3698)

Variables	Hearing loss No./ Participants No.	ModelA[b]		Model B[c]		Model C[d]	
Cadmium							
Per doubling of Cadmium		1.28	(1.09, 1.50)	1.26	(1.07, 1.49)	1.26	(1.07, 1.47)
Cadmium Quintile *(ug/L)*							
Quintile 1 (0.10-0.20)	71/1047	1	(Reference)	1	(Reference)	1	(Reference)
Quintile 2 (0.30-0.30)	53/566	1.20	(0.71, 2.05)	1.17	(0.69, 1.99)	1.21	(0.71, 2.05)
Quintile 3 (0.40-0.40)	72/593	1.07	(0.72, 1.58)	1.01	(0.68, 1.50)	1.05	(0.71, 1.55)
Quintile 4 (0.50-0.70)	128/796	1.44	(0.96, 2.16)	1.39	(0.92, 2.11)	1.39	(0.91, 2.11)
Quintile 5 (0.80-8.50)	117/696	1.80	(1.14, 2.85)	1.72	(1.08, 2.76)	1.74	(1.12, 2.70)
P-Trend		*0.009*		*0.017*		*0.013*	
Lead							
Per doubling of Lead		1.13	(0.98, 1.30)	1.11	(0.96, 1.28)	1.09	(0.95, 1.26)
Lead Quintile *(μg/dL)*							
Quintile 1 (0.20-0.80)	21/659	1	(Reference)	1	(Reference)	1	(Reference)
Quintile 2 (0.90-1.30)	61/872	1.10	(0.57, 2.10)	1.12	(0.58, 2.15)	1.08	(0.55, 2.12)
Quintile 3 (1.40-1.80)	80/689	1.14	(0.62, 2.09)	1.14	(0.61, 2.11)	1.10	(0.58, 2.05)
Quintile 4 (1.90-2.70)	115/738	1.28	(0.72, 2.27)	1.26	(0.70, 2.27)	1.21	(0.67, 2.22)
Quintile 5 (2.80-54.00)	164/740	1.48	(0.84, 2.62)	1.43	(0.80, 2.57)	1.36	(0.75, 2.48)
P-Trend		*0.041*		*0.084*		*0.120*	

[a]Hearing loss was defined as pure tone average at speech frequencies (0.5, 1, 2, and 4 kHz) > 25 dB.
[b]Model A was adjusted for age, age^2, sex, race/ethnicity, education, body mass index, ototoxic medication, pack-years of cigarette smoke, hypertension, and diabetes. Cadmium models were further adjusted for lead; lead models were further adjusted for cadmium.
[c]Model B: Model A + further adjusted for occupation noise.
[d]Model C: Model B + further adjusted for recreation noise, and firearm noise.

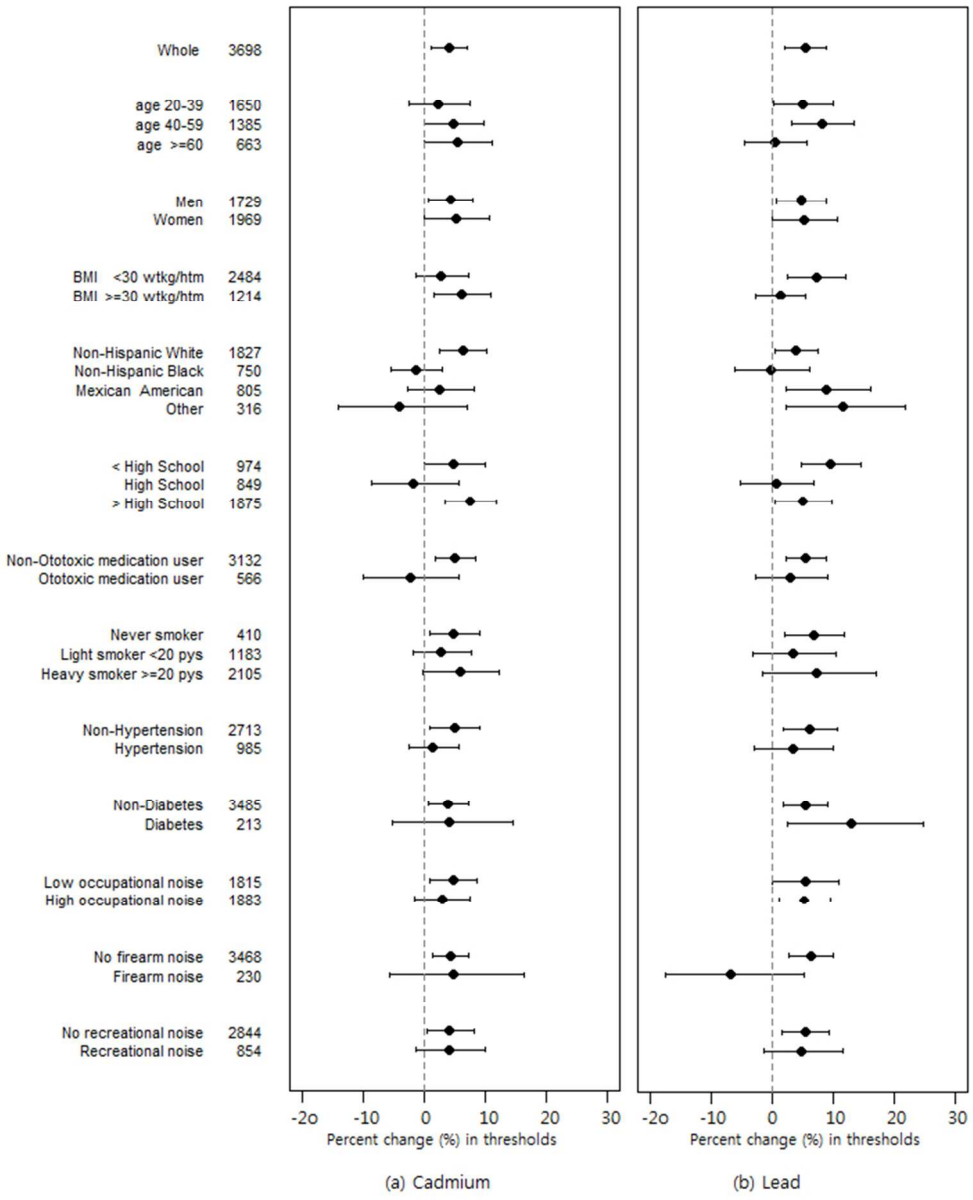
Table 4. Percent change (95% CIs) in hearing thresholds (dB) by joint effect between blood cadmium and lead levels (N=3698)

Variables	Low Cd	High Cd	Percent change (95% CIs) for Cd within strata of Pb
	Percent change (95% CIs)	Percent change (95% CIs)	
Low Pb	0 (Reference)	7.33 (0.38, 14.77) *p=0.044*	7.33 (0.38, 14.77) *p=0.044*
High Pb	10.09 (0.35, 20.78) *p=0.048*	19.01 (9.68, 29.13) *p<0.001*	8.1 (-0.87, 17.87) *p=0.085*
Percent change (95% CIs) for Pb within strata of Cd	10.09 (0.35, 20.78) *p=0.048*	10.88 (3.40, 18.90) *p=0.006*	

Measure of interaction on additive scale: RERI=1.6%; 95% CI: -9.4, 12.6%; *p=0.778*.
Measure of interaction on multiplicative scale: percent change of interaction term=0.7%; 95% CI: -8.9, 11.39%; *p=0.891*.
Models were adjusted for age, age^2, sex, race/ethnicity, education, body mass index, ototoxic medication, cumulative cigarette pack-years, current dx of hypertension, current dx of diabetes, and occupation, recreation, and firearm noise. Cadmium models were further adjusted for lead; lead models were further adjusted for cadmium.

FIGURE LEGEND

Figure 1. Multivariate-adjusted percent change (95% CIs) in hearing thresholds (dB) per doubling of cadmium and lead by participant characterisctics



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